

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/004734 A1

- (51) International Patent Classification⁷: **A61K 31/519**, A61P 1/00 (74) Agent: GILL, Jennings & Every; Broadgate House, 7 Elton Street, London EC2M 7LH (GB).
- (21) International Application Number: PCT/GB2003/002974 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 9 July 2003 (09.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0216027.3 10 July 2002 (10.07.2002) GB
0304648.9 28 February 2003 (28.02.2003) GB
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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Published:

— with international search report

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WO 2004/004734 A1

(54) Title: 4-(2-FLUOROPHENYL)-6-METHYL-2-(1-PIPERAZINYL)THIENO(2,3-D) PYRIMIDINE IN THE TREATMENT OF FUNCTIONAL BOWEL DISORDER

(57) Abstract: Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of a functional bowel disorder.

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4- (2-FLUOROPHENYL) -6-METHYL-2- (1-PIPERAZINYL) THIENO (2,3-D) PYRIMIDINE IN THE
TREATMENT OF FUNCTIONAL BOWEL DISORDER

Field of the Invention

This invention relates to a new use for a known compound.

5. Background of the Invention

4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine
monohydrate hydrochloride is known (see US-A-4695568) and has shown activity as
an antidepressant. It has serotonin and noradrenergic reuptake blocking properties and
this is thought to be the mechanism for its action as an antidepressant. The compound
10 also has 5HT-3 blocking activity.

Functional bowel disorders are very common and include irritable bowel
syndrome (IBS) and functional dyspepsia. IBS is the most common disorder diagnosed
by gastroenterologists and one of the more common encountered in general practice.
The overall prevalence rate is similar (approx 10%) in most industrialised countries.
15 Some estimates of prevalence have reached 20%. The illness has a large economic
impact on health care use and indirect costs, chiefly through absenteeism.

IBS falls into two categories of equal prevalence, constipation-predominant and
diarrhoea-predominant. The available treatments are generally poor.

A recent approach to treating diarrhoea-predominant IBS has involved the use
20 of alosetron. This drug works by blocking the 5HT-3 receptor. Other drugs with this
mechanism of action have shown some limited activity in this disease, including
granisetron. Alosetron, although effective, was withdrawn due to side-effects on the
colon.

A recent approach to treating constipation-predominant IBS involved agonising
25 the 5HT4 receptor. Two such agonists are in clinical trials, i.e. tegaserod and
prucalopride. Other approaches being explored include using 5HT1 agonists such as
buspirone.

Functional dyspepsia is characterised by impaired accommodation of the
stomach to a meal and epigastric pain discomfort or pain. There is often early satiety
30 and weight loss. The disorder is not well understood. Treatments include
antispasmodics and drugs affecting gut motility. Early studies suggest that buspirone
and serotonin reuptake inhibitors may be useful.

Summary of the Invention

Surprisingly, it has been found that the known compound identified above
35 (referred to herein as MCI-225) has activity in the treatment of functional bowel

disorders. Its combination of serotonin and noradrenergic reuptake blockade and 5HT-3 receptor blockade has not previously been clearly identified as being responsible for activity in functional bowel disorders. Furthermore MCI-225, at doses effective in the treatment of bowel disorders, can produce a lower incidence of some of the side-effects which are commonly known to be associated with the clinical use of selective serotonin reuptake inhibitors, for example the production of nausea and vomiting or the induction of sexual dysfunction. It will be appreciated that any suitable form of the active principle may be used, e.g. another salt form, or a prodrug or active metabolite.

Description of Preferred Embodiments

10 By means of this invention, functional bowel disorders and associated pain symptoms can be treated, e.g. controlled or prevented. Such disorders include irritable bowel syndrome, including diarrhoea-predominant, constipation-predominant, and alternating constipation/diarrhoea IBS. The patient may be male or female, diarrhoea-predominant IBS being particularly associated with women.

15 For use in the invention, the active compound can be formulated in any suitable manner together with a conventional diluent or carrier. The active compound is preferably administered by the oral route; other suitable routes of administration include sublingual/buccal, transdermal, intramuscular, intranasal, rectal, parenteral, subcutaneous, pulmonary and topical. An effective dose of the active agent will depend on the nature and degree of the complaint, the age and condition of the patient and other factors known to those skilled in the art. A typical daily dosage may be 0.1 mg to 1 g.

A pharmaceutical composition containing the active ingredient may be in the form of a sublingual tablet or patch. Suitable compositions for oral use include tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups and elixirs. Suitable additives include sweetening agents, flavouring agents, colouring agents and preserving agents. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, e.g. inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as

glyceryl monostearate or glyceryl distearate may be employed. They may also be coated, to form osmotic therapeutic tablets for controlled release. Hard gelatin capsules may include an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin; soft gelatin capsules may include water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

The data on which this invention is based will now be described. In a study using intact animals, the ability of a drug to inhibit the reflex depressor response to colorectal distension can be assessed. In this model, an inhibition of the reflex indicates modulation of visceral nociceptive neurotransmission and, therefore, the use of the drug in functional bowel disease (e.g. IBS); see Kozłowski *et al*, 2000, Gut 46, 474-480. Allodynia and visceral pain are important components of functional bowel disease.

Study

Experiments were performed on male Sprague-Dawley rats (250-300 g). Anaesthesia was induced with isoflurane (2.5% in oxygen) and maintained with alpha chloralose (80 mg/kg i.v.). The left carotid artery was cannulated for the measurement of blood pressure and heart rate and the left jugular vein cannulated for drug administration. A tracheal cannula was implanted for artificial respiration if required. A 10 mm long latex balloon was inserted intrarectally so that the tip of the balloon was 20 mm from the anal verge (Kozłowski *et al*, *supra*). The balloon was connected via a double lumen cannula to a pressure transducer and also to a saline-filled syringe for inflation/deflation of the balloon. Throughout the experiment, body temperature was kept constant at 36-38 C using a homeothermic blanket.

Once stable baseline parameters were obtained (approximately after 20 minutes), the balloon was rapidly inflated with increasing volumes of saline (0.5-2.5 ml) for 30 seconds at 5 minute intervals, and the resultant change in blood pressure recorded. Three distinct response curves were constructed, with a 10 minute stabilisation period between each curve. In one group of animals, 10 minutes prior to the commencement of the final distension response curve, a single bolus of MCI-225 (3 mg/kg) was administered intravenously; in a second group of animals, a single bolus dose of vehicle was administered. The effect of MCI-225 and vehicle was determined by analysing the changes in colorectal distension that evoked depressor response.

Falls in arterial blood pressure (mean absolute decreases in mean arterial pressure in mmHg, with standard error of mean in brackets) evoked by distension of the balloon, before adding drug, at 0.5, 1.0, 1.5, 2.0 and 2.5 ml balloon volume were 2.7

(1.9), 12.4 (5.9), 24.0 (8.9), 36.3 (4.8) and 43.4 (6.0), respectively (all except final value n=6, final value n=5). Following administration of MCI-225 at 3 mg/kg i.v., the corresponding values were 2.2 (1.65), 6.3 (2.6), 10.6 (3.9), 15.3 (5.4) and 24.6 (7.3), respectively (all values except final value n=6, final value n=5).

- 5 The results clearly show that MCI-225 inhibited the distension-induced falls in blood pressure. The falls in blood pressure evoked by 2.0 and 2.5 ml balloon volumes were reduced with statistical significance following administration of MCI-225 at 3mg/kg, with p values (paired t test) of less than 0.01 and less than 0.05 respectively.

CLAIMS

1. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of a functional bowel disorder.
- 5 2. Use according to claim 1, wherein the salt is the hydrochloride monohydrate.
3. Use according to claim 1 or claim 2, wherein the disorder is irritable bowel syndrome.
4. Use according to claim 3, wherein the disorder is diarrhoea-predominant irritable bowel syndrome.
- 10 5. Use according to claim 4, wherein the disorder is in a female patient.
6. Use according to claim 3, wherein the disorder is alternating constipation/diarrhoea irritable bowel syndrome.
7. Use according to claim 3, wherein the disorder is constipation-predominant irritable bowel syndrome.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/02974

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/519 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EGUCHI J ET AL: "The anxiolytic-like effect of MCI-225, a selective NA reuptake inhibitor with 5-HT3 receptor antagonism" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, ELSEVIER, US, vol. 68, no. 4, April 2001 (2001-04), pages 677-683, XP002239887 ISSN: 0091-3057 abstract --- -/-	1-7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

1 October 2003

Date of mailing of the international search report

17/10/2003

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CROWELL M D: "The role of serotonin in the pathophysiology of irritable bowel syndrome" AMERICAN JOURNAL OF MANAGED CARE 2001 UNITED STATES, vol. 7, no. 8 SUPPL., 2001, pages S252-S260, XP009018426 ISSN: 1088-0224 the whole document	1-7
Y	US 6 284 770 B1 (MANGEL ALLEN WAYNE ET AL) 4 September 2001 (2001-09-04) the whole document	1-7
A	DE 100 63 223 A (MERCK PATENT GMBH) 20 June 2002 (2002-06-20) abstract page 2, line 43	1-7
A	US 4 695 568 A (NINOMIYA KUNIHIRO ET AL) 22 September 1987 (1987-09-22) cited in the application the whole document	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 03/02974

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6284770	B1	04-09-2001	AU 750818 B2	25-07-2002
			AU 9629398 A	27-04-1999
			BR 9812886 A	08-08-2000
			CA 2305751 A1	15-04-1999
			EE 200000214 A	15-06-2001
			EP 1021174 A2	26-07-2000
			HR 20000198 A1	30-04-2001
			HU 0003750 A2	28-10-2001
			JP 2001518495 T	16-10-2001
			NO 20001776 A	06-06-2000
			NZ 503698 A	25-10-2002
			PL 340337 A1	29-01-2001
			SK 4862000 A3	18-01-2001
			CN 1281357 T	24-01-2001
			WO 9917755 A2	15-04-1999
			TR 200000913 T2	22-01-2001
			US 2003036549 A1	20-02-2003
			US 2001044450 A1	22-11-2001
			ZA 9809061 A	05-07-2001
DE 10063223	A	20-06-2002	DE 10063223 A1	20-06-2002
			AU 2795702 A	01-07-2002
			CA 2431074 A1	27-06-2002
			CZ 20031754 A3	17-09-2003
			WO 0249650 A2	27-06-2002
			EP 1347761 A2	01-10-2003
			NO 20032772 A	18-06-2003
US 4695568	A	22-09-1987	JP 1699365 C	28-09-1992
			JP 3067071 B	21-10-1991
			JP 60146891 A	02-08-1985
			AT 35137 T	15-07-1988
			CA 1224782 A1	28-07-1987
			DE 3472106 D1	21-07-1988
			DK 617184 A ,B,	06-07-1985
			EP 0150469 A1	07-08-1985
			HU 37435 A2	28-12-1985